10151 K/05 B07 BEEC 10.07.81
BEECHAM GROUP PLC *EP --70-127
10.07.81-GB-021302 *(19.01.83)* A61k-09/20 A61k-47

Tablets of poorly compressible material - contg. plasticiser to allow compression to be effected using conventional pressure

C83-009932 D/S:E(CH DE FR GB IT LI NL)

A tablet comprises a poorly compressible ingredient (I) and a plasticiser (II) incorporated into the tablet body.

Pref. (I) is a high dose medicament which represents at least 50 wt.% of the tablet; (II) is propylene glycol, liq. polyethylene glycol, glycerine, hexylene glycol, 1,2,6-trihydroxyhexane, solketal or diethyl phthalate and represents 0.1-2 wt.% of the tablet; and the tablet further includes 0.1-10 wt.% of binder, esp. 2-5 wt.% of water-soluble binder.

ADVANTAGE

Inclusion of (II) greatly increases the strength of the tablets formed at conventional compression pressures, greatly decreases their friability, but at the same time does not have a detrimental effect on their disintegration.

DETAILS

The binder is pref. a water-sol. material such as PVP, gelatin, methyl hydroxyethyl cellulose, hydroxypropyl methyl cellulose or hydrolysed gelatin. Alternatively, a water-insol. material such as ethyl cellulose can be used to give a sustained release tablet.

The tablet is formed by mixing (I) and (II) prior to compression, and then compressing the mixt. Pref. (II) is added to a soln. of binder, the resultant soln. is added to (I) and the obtd. wet mix is formed into a dry powder/granulate conventionally, e.g. by wet granulation, spray granulation or spray drying. The obtd. powder or granular prod. is then compressed into tablets.

EXAMPLE

Paracetamol (476.5g) and Explotab (RTM; sodium starch glycollate; disintegrant) (10g) were blended in a tumbler mixer for 5 mins. Kollidon 90 (RTM; polyvinylpyrrolidone; binder) (10g) was then added as an 8% w/v aq. soln which also contained 1 g of propylene glycol. The resultant mixt. was mixed in a planetary mixer for 10 mins., wet screened through a 1.7 mm screen, dried at 50°C overnight and dry screened through a 1.0 mm screen. A 1000-200 µm sieve cut of the granules was blended with 0.5 wt.% Mg stearate and compressed into 200 mg tablets at conventional pressures of 30-150 MN/m^2.(13pp914).

(E)ISR:No Search Report.

B(4-C3C, 7-A4, 10-E4C, 10-G2, 12-M11) 5 053

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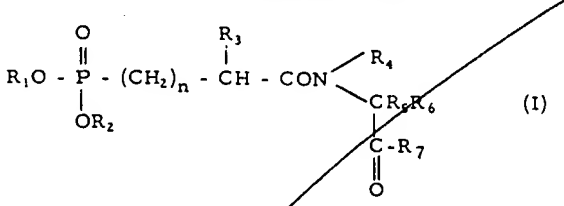
53 K/05 B05 ANAL-09.07.81
ANALYT RES PHARM PT *EP --70-131
08.04.82-AU-003542 (+009682) *(19.01.83)* A61k-31/67 C07f-09/38

Antihypertensive phosphono:alkanol:aminoacid cpds. - esp. useful for redn. of angiotensin related hypertension

C83-009934 Intermediate priority: 13.11.81-AU-001560.

D/S: E(CH DE FR GB IT LI SE).

Phosphonoalkanoylamino acid cpds. of formula (I) and their pharmaceutically acceptable salts, are new:



(I)

(R_1, R_2 and R_3 are each H, opt.substd. lower alkyl, lower alkenyl, or opt.substd. aryl or aralkyl;
n 0 or 1; and

B(5-B1E, 5-B1F, 5-B1G, 12-A1, 12-A6, 12-F5, 12-G1, 12-G7) 6 054

(a) R_4 is H, lower alkyl or phenyl-lower alkyl; R_5 and R_6 are each H, opt.substd. lower alkyl, or aryl; and R_7 is $-OR_8$, $-NR_9$ (sic) or $-SR_{10}$ where R_8 and R_{10} are each H, lower alkyl or opt.substd. aryl or aralkyl, and R_9 is H, OH, lower alkyl or the residue of an α-amino acid; or
(b) R_4 and R_5 together form an opt.substd. bridge of 2-4 atoms of C or C with O, N or S; and R_6 and R_7 are as in (a); with the proviso that when R_3 is H, n is 0, the heterocyclic ring is an unsubstd. pyrrolidine, R_6 is H and R_7 is OR_8, at least one of R_1, R_2 and R_8 is opt.substd. aryl; or
(c) R_5 and R_6 are such as to form an α-amino acid side chain so that $N(R_4)CR_5R_6COR_7$ is an α-amino acid residue; with the proviso that (i) when R_3 is H and n is 0, the residue is not alanine, aspartic acid, glutamic acid, glycine or phenylalanine, and (ii) when R_3 is H and n is 1, the residue is not aspartic acid; or
(d) R_5 and R_6 are part of a 3-6C cycloalkyl ring; and R_4 and R_7, where appropriate, are as in (a)).

USES/ADVANTAGE

(I) are antihypertensive agents, esp. useful for reduction of angiotensin related hypertension. They may also be

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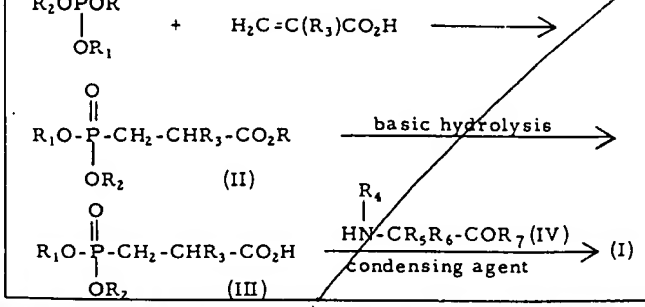
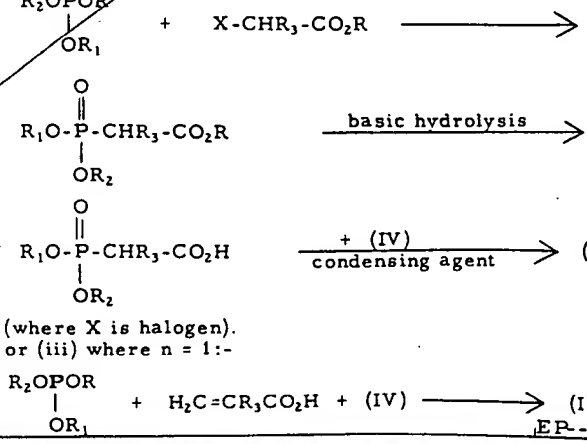
useful as antibacterial, anticancer and antiviral agents. The prefd. (I) (in which R_7 is OR_8) are angiotensin converting enzyme inhibitors which are superior to mercaptoalkanoyl amino acid inhibitors since they lack the toxicity associated with the SH gp. (I) are more stable towards hydrolysis than known N-phosphorylated dipeptides and related cpds. Antihypertensive doses are e.g. 0.5-500 mg/kg/day, pref. in 2-4 units. Parenteral admin. is prefd.

PREPARATION

(i) where n = 1:-



(where X is halogen).
or (iii) where n = 1:-



(where R is lower alkyl, aryl or aralkyl).
Opt. (III) is converted to the acid chloride before amide formation.
(ii) where n = 0:-

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